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Bispidine derivative as a class III anti-arrythmic.

Formula 1 bispidine

[DIAGRAM]

where
R, R^1 and R^3 are the same or different and represent H, C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy and
when

O
↓
Y = - C-,

R^2 represents C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy, - $NHSO_2CH_3$, $-CF_3$, NH-acetyl and $-NR^4R^5$, where R^4 and R^5 are C_1-C_4-alkyl and represent C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy, $-NHSO_2CH_3$, $-CF_3$, NH-acetyl and $-NR^9R^{10}$ when

O
↓
Y = - C-NH-,

Where NR^9 represents C_1-C_4-alkyl and R^{10} represents H or C_1-C_4-alkyl and R^2 can also be NO_2 and NH_2 when X = CH_2.
X represents $-CH_2$-, -C(O)- or $-C(R^6)OR^7$- (where R^6 represents H, C_1-C_4-alkyl and R^7 represents H, C_1-C_4-alkyl and

[DIAGRAM]

with R^8 representing H, C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy),
Y can be -C(O)- or -CONH- and
Z can be , C_1-C_4-alkyls, which are unsaturated and/or can be branched, as well as their physiologically digestible salts.

Bispidine derivatives as a class III anti-arrhythmic

The invention concerns new bispidine derivatives, the medicine contained within them and their use in manufacturing a class III anti-arrythmic (Vaughn Williams).

The anti-arrhythmics are divided into 4 groups for reasons of Vaughn Williams's classification: 1.) sodium antagonists, 2.) adrenergic beta receptor blockers, 3.) potassium canal inhibitors, 4.) calcium antagonists.

Bispidine derivatives are known as anti-arrythmics (Peter C. Ruenitz and Corwin M. Mokler, J. Med. Chem., 22, 1142 (1979), EP-A-62 199; DE-A-27 26 571) They belong largely to the (Vaughn Williams) class I of sodium antagonists on the basis of their effective mechanism. Ambasilide (EP-A-62 199) however demonstrates a class III effect.

Class III anti-arrythmics are often preferred in therapy, as they are effective against arrythmia which resists other forms of therapy. Class III anti-arrythmics promote delay in the QT stretch in ECG, without affecting the PQ duration and without a strong drop in the heart frequency.

Such anti-arrythmics are laid out for example in EP-A-164 165, EP-A-178 874 and EP-A-158 775.

It has now been discovered that formula 1 bispidine derivatives

[DIAGRAM]

where
R, R^1 and R^3 are the same or different and represent H, C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy and
when

O
↓
Y = - C-,

R^2 represents C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy, - $NHSO_2CH_3$, $-CF_3$, NH-acetyl and $-NR^4R^5$, where R^4 and R^5 are C_1-C_4-alkyl and represent C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy, $-NHSO_2CH_3$, $-CF_3$, NH-acetyl and $-NR^9R^{10}$ when

O
↓
Y = - C-NH-,

Where NR^9 represents C_1-C_4-alkyl and R^{10} represents H or C_1-C_4-alkyl and R^2 can also be NO_2 and NH_2 when X = CH_2.
X represents $-CH_2$-, -C(O)- or $-C(R^6)OR^7$- (where R^6 represents H, C_1-C_4-alkyl and R^7 represents H, C_1-C_4-alkyl and

[DIAGRAM]

with R^8 representing H, C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy),
Y can be -C(O)- or -CONH- and
Z can be , C_1-C_4-alkyls, which are unsaturated and/or can be branched, as well as their physiologically digestible salts have superior qualities.

R^3 is preferably hydrogen, X -CH2- and -CO-, Y -CONH- and Z methylene.

The inventive reagents can be produced for example according to the following reaction plans A to C:

[DIAGRAM: Reaction plan A]

The N-monobenzylbispidine from DE-A 27 26 571 is shifted to amide according to the normal methods using a correspondingly substituted benzoylchloride, the benzyl groups split hydrogenating and the remaining secondary amino groups are shifted to the end product I with a reagent

[DIAGRAM]

where R, R^1 and Z have the above meaning and A represents an exit group. The exit group A, which exits via the nucleophile, can be, for example, a chlorine or bromine atom, a methoxy or ethoxy group, a residual oxisuccinimide, 1-imidazolyl or ethoxycarbonyloxy.

[DIAGRAM: Reaction plan B]

This is one of the several possibilities for producing general formula 1 reagents with a carbamide grouping (cf. Houben-Weyl, Meth. D. org. Ch., 4th edition, E4, pg. 334ff). With reagents I made in this way, the residual benzyl can be exactly substituted with the residual R and R^1.

[DIAGRAM: Reaction plan C]

N, N- dibenzylbispidone is partially debenzylised (cf. Example 28), benzylised as above (A) and then transferred to a general formula 1 reagent. The residual benzyl can be exchanged again here for another residue

[DIAGRAM]

and the carbonyl group can be e.g. reduced with sodium boranate or with a Grignard reagent and the remaining hydroxyl group can be esterified or etherified using the normal methods.

If R^2 shows a primary or secondary amino group in these various synthesis possibilities, this can for example protect against acetylisation and further hydrolytically divide depending on further molecule shifts.

If necessary, the bispidine derivatives concerned are transferred to the acid addition salt of a physiologically digestible acids. A compilation of normal physiologically digestible acids can be seen in the Fortschritte der Arzneimittelforschung (advances of medical research) 1966, Birkhaeuser Verlag, Bd. 10, pgs. 224 to 285, Germany, Switzerland.

It is known that the acid addition salts are generally produced through mixing free bases or their solutions with the corresponding acid or their solutions in an organic solvent, for example a low alcohol such as methanol, ethanol or propanol; or a low ketone such as acetone, methylethylketone or methylisobutylketone, or an ether such as diethylether, tetrahydrofurane or dioxane. Mixes of the above solutions can be used to better separate the crystals. Moreover, pharmaceutically justifiable diluted acid addition salt solutions of formula I bispidine derivatives are produced by dissolving free bases into a diluted acid solution.

The invention concerns additional therapeutic methods for topical and above all systematic use, which include a reagent of formula I to normal catalysts or flux as

biocatalysts, and the use of a reagent to formula I to produce a medicine, in particular an anti-arrythmic.

The new reagents have, as the study below shows, a good class III anti-arrhythmic effect:

Animals used in the test were male and female Pirbright white guinea pigs within the weight range of 300 – 500gr. The anaesthetic used was 1.5g/kg of urethane i.p. Substances were administered intravenously. The II. limb lead was used to measure the ECG lead times and the heart frequency. The measuring quantities are the QT and PQ lines and the heart frequency. Between 4 and 6 animals were used per dosage. Criteria for class III effect are an increase in the QT length in comparison to the values before the substance was added. PQ increases and strong heart decreases are used as exclusion criteria. The ED 20% is calculated from the linear relationship between the log dose (mg/kg) of the substance and the relative extension of the QT length (Δ%).

Table 1

Anti-arrythmic class III effect in guinea pigs after intravenous application	
Example no.	Extension of QT length ED 20% (mg/kg) Mean
2	4.6
21	2.6
23	2.4
26	3.6
Ambasilide	6.3
D-Sotalol	3.6

The substances according to the invention (table 1) are, in view of the QT extension, considered to be more effective than the anti-arrythmic ambasilide and to an extent as the known class III anti-arrythmic D-Sotalol (Clin. Sci. 69, 631-636 (1985); J. Cardiovascul. Pharmacol., 6, 1132-1141 (1984)).

The new substances are suitable for the treatment of arrhythmia, which are otherwise resistant to therapy, in particular, they reduce ventricular tachycardia, which occurs after myocardial infarction and relies on a "re-entry" mechanism (Lit. Cardiac Arrhythmia Ed. P. Brugada, H.J.J. Wellens, Futura Publishing Co., Mount Kisko, New York 1987).

Therapeutic methods or preparations are produced with the normal fluid or solid catalysts or flux and the pharmaceutical technical auxiliary materials used in the normal way and corresponding to the required application method and a suitable dosage, usually by mixing the biocatalysts with the catalysts and auxiliary materials normally found in such preparations.

The medicine can be administered orally, para-orally or topically. The current preparations are e.g. tablets, film tablets, coated tablets, capsules, pills, powder, solutions or suspensions, infusions or injection solutions as well as pastes, ointments, gels, creams, lotions, poudrage, solutions or emulsions and sprays.

The therapeutic methods can include the reagents to be used according to the invention in local use in 0.0001 to 1% concentrations, preferably in 0.001 to 1% concentrations. For systematic use, a single dose of 0.1 to 20mg per kg weight per day

in one or more doses is recommended (0.1 to 4mg per kg weight para-orally and 1 to 20mg per kg weight orally), depending on the type and severity of the illness.

Normally, the pharmaceutical technical auxiliary materials used for local use are e.g. alcohol, ethanol, isopropanol, oxethylised ricinus oil or oxethylised hydrated ricinus oil, polyacrylic acid, glycerinmonostearate, paraffin oil, vaseline, lanolin, polyethylene glycol, stearates such as ethoxylised fat alcohol. The materials used for systematic use are lactose, propylene glycol and ethanol, starch, talc, polyvinylpyrrolidone. If necessary, an anti-oxidant can be added to the preparations, i.e. tocopherol such as butylised hydroxyanisol or butylised hydroxytoluol or flavours, stabilisers, emulsifiers, bleaching agents etc. This requires that all pharmaceutical ingredients used by the manufacturer are not toxicologically damaging and are tolerated by the catalysts used.

Example 1

3-(4-Acetaminobenzoyl)-7-benzyl-3.7-diazabicyclo[3.3.1]nonan

80.2g (0.24 mol) of 3-(4-Acetaminobenzoyl)-7-benzyl-3.7-diazabicyclo[3.3.1]nonan is dissolved in 500ml of anhydrous tetrahydrofurane and cooled using ice. 23.5g (0.3 mol) of acetyl chloride is then added, dissolved in 50ml of tetrahydrofurane, and then 48.6g (0.48 mol) of triethylamin is added at room temperature. The solution is left overnight to settle. The solution is then constricted by vacuum. The residue is absorbed in water and extracted (x 3) using methylene chloride. The united organic phases are washed with water, dried and constricted in the vacuum. Result: 78.1g, M.P.: 208°C.

Example 2

7-benzyl-3-(4-chlorbenzoyl)-3.7-diaza-bicyclo[3.3.1]-nonanhydrochloride

5g (23 mmol)of monobenzyl bispidine is dissolved in 100ml methylene chloride and mixed with 20ml of 2 M NaOH. When cooling with ice and allowing to settle for a long period, 4.9g (28 mmol) of 4-chlorbenzoylchloride, dissolved in 10ml of methylchloride is added. The solution is left to settle for 1 hour, then diluted with water and the methylene chloride phase is isolated, which is later washed again with water, dried and mixed with ether HCl. The oil obtained crystallises to acetic ester/ether. Result: 4.9g, M.P.: 166°C (x2HCl).

The following reagents are produced by the analogue example 2:

3. 7-benzyl-3-(2-methoxybenzoyl)-3.7-diaza-bicyclo[3.3.1]nonanhydrochloride, M.P.: 162°C (xHCl)
4. 7-benzyl-3-(2-chlorbenzoyl)-3.7-diaza-bicyclo[3.3.1]nonan, M.P. 266°C (x2HCl).
5. 7-benzyl-3-(4-dimethylaminobenzoyl)-3.7-diaza-bicyclo[3.3.1]nonan, M.P.: 66°C (x2HCl)
6. 7-benzyl-3-(4-methoxybenzoyl)-3.7-diazabicyclo[3.3.1]nonan, M.P. 119°C (xHCl)
7. 7-benzyl-3-(4-cyanbenzoyl)-3.7-diazabicyclo[3.3.1]nonan, M.P. 170°C (x2HCl)
8. 7-benzyl-3-(2-methlbenzoyl)-3.7-diazabicyclo[3.3.1]nonan, M.P. 243°C (xHCl)

9. 7-benzyl-3-(4-brombenzoyl)-3.7-diazabicyclo[3.3.1]nonan, M.P. 166°C (x2HCl)
10. 7-benzyl-3-(4-methylbenzoyl)-3.7-diazabicyclo[3.3.1]nonan, M.P. 133°C (x2HCl)
11. 7-benzyl-3-(4-fluorbenzoyl)-3.7-diazabicyclo[3.3.1]nonan, M.P. 133°C (x2HCl)
12. 7-benzyl-3-(4-trifluormethlbenzoyl)-3.7-diazabicyclo[3.3.1]nonan, M.P. 89°C

Example 13

3-(3-aminobenzoyl)-7-benzyl-3.7-diazabicyclo[3.3.1]nonan

10g (46 mmol) is dissolved in 100ml methylene chloride and mixed with 20ml 2 M sodium hydroxide. When cooling with ice and allowing to settle, 9g (48.5 mmol) of 3-nitrobenzoylchloride, dissolved in 30ml of methylene chloride, is added. The solution is left to settle for 1 hour and then the organic phase is separated, which is then washed with water, dried and constricted in the vacuum. 11.5g of 7-benzyl-3-(3-nitrobenzoyl)-3.7-diabicyclo[3.3.1]nonan is obtained.

10.5g (28.8 mmol) of this nitro derivative is dissolved in 250ml of methanol, mixed with 0.5g platinum/carbon (5%) and hydrated until all hydrogen is absorbed. The catalyst is then filtered and the filtrate is constricted in the vacuum. The residue is dissolved in methylene chloride , washed with sodium chloride and water, dried and mixed with ether HCl. An oil is isolated, which crystallises to acetone. Result: 9.75g, M.P. 235°C (x2HCl).

The following are produced by analogue example 13:

14. 3-(4-amino-2-chlorbenzyl)-7-benzyl-3.7-diazabicyclo[3.3.1]nonan, M.P. 213°C (x2HCl)
15. 3-(2-aminobenzoyl)-7-benzyl-3.7-diazabicyclo[3.3.1]nonan, M.P. 178°C

Example 16

3-(4-aminobenzoyl)-7-(4-chlorbenzyl)-3.7-diabicyclo[3.3.1]nonan

78.0g (0.21 mol) of 3-(4-acetaminobenzoyl)-7-benzyl-3.7-diazabicyclo[3.3.1]nonan (cf. example 1) is dissolved in 1.3l of methanol and mixed with 3.0g of palladium/carbon (10%). It is hydrated for equimolar hydrogen use. The reaction mixture is filtered and the filtrate constricted in the vacuum. Crystallised 3-(4-acetaminobenzoyl)-3.7-diazabicyclo[ ]3.3.1]nonan is obtained. Result: 59g, M.P.: 186 to 189°C.

5.0g of this product is dissolved together with 3.6g (17.5 mmol) of 4-chlorbenzylbromide and 5ml triethylamine in 100ml of methanol and left for 60 hours at 25°C. It is then constricted in the vacuum and the residue dissolved in methylene chloride. The organic phase is washed with 2 M sodium chloride and water, dried and constricted in the vacuum. 6.6g of 3-(4-acetaminobenzoyl)-7-(4-chlorbenzyl)-3.7-diaza-bicyclo[3.3.1]nonan is obtained. M.P.: 181°C.

6.6g (16 mmol) of the above product is dissolved in 50ml of methanol and mixed with 60ml of 0.1 M sodium chloride. This is heated at 100°C for 3 hours. The resulting precipitate is isolated and re-crystallised to toluol/ethanol. Result: 2.3g. M.P.: 255°C.

The following reagents from 3-(4-acetaminobenzoyl)-3.7-diazabicyclo[3.3.1]-nonan are made by analogue example 16:

17. 3-(4-aminobenzoyl)-7-(3-cinnamyl)-3.7-diazabicyclo[3.3.1]nonan, M.P. 194°C (x2HCl)
18. 3-(4-aminobenzoyl)-7-(2-phenylethyl)-3.7-diazabicyclo[3.3.1]nonan, M.P. 167°C
19. 3-(4-aminobenzoyl)-7-(2.6-dichlorbenzyl)-3.7-diazabicyclo[3.3.1]nonan, M.P. 213°C

Example 20

7-benzyl-3-(methansulphonylamido)-3.7-diazabicyclo[3.3.1]nonan

At 5-10°C, add 1.9g (16.4 mmol) methansulphonylchloride to 5.0g (14.9 mmol) of 3-(4-amniobenzoyl)-7-benzyl-3.7-diabicyclo[3.3.1]nonan, which has been dissolved in 50ml of pyridine. This is left for 16 hours to settle at the current temperature. The reaction mixture is cast into 200ml water, where the product separates, and is then removed from the water through decanting. The resulting product is crystallised to acetic ester. Result: 4.1g, 172°C.

Example 21

7-benzyl-3-(4-methylphenylcarbamoyl)-3.7-diazabicyclo[3.3.1]nonan

2.6g (0.012 mol) of monobenzylbispidine, 1.6g (0.012 mol) of 4-methylphenylisocynate and 0.25ml of triethylamin are dissolved in 25ml of ligroin and are warmed to the backflow temperature. The resulting precipitate is isolated and re-crystallised to ligroin/2-propanol. Result: 2.5g, M.P.: 157°C.
The following reagents from monobenzylbispidine are made by example 21:

22. 7-benzyl-3-(4-methophenylcarbamoyl)-3.7-diaza-bicyclo[3.3.1]nonan, M.P. 161°C
23. 7-benzyl-3-(4-chlorphenylcarbamoyl)-3.7-(2-phenylethyl)-3.7-diaza-bicyclo[3.3.1]nonan, M.P. 175°C
24. 7-benzyl-3-(phenylcarbamoyl)-3.7-dichlorbenzyl)-3.7-diaza-bicyclo[3.3.1]nonan, oil

Example 25)

3-(4-aminophenylcarbamoyl)-7-benzyl-3.7-diaza-bicyclo[3.3.1]nonan

5.2g (24 mmol) of monobenzylbispidine, 3.95g (24 mmol) of 4-nitrophenylisocate and 0.50ml of triethylamine are added to 50ml of Ligroin and then warmed for 1 hour at the backflow temperature. The resulting precipitate is isolated and re-crystallised to methanol/isopropanol. Result: 6.7g.

5.6g (14.7 mmol) of the resulting nitro reagent is placed in 100ml methanol, mixed with 0.6g platinum/carbon (5%) and hydrated at RT and 1 bar. This is then filtered and the filtrate constricted in the vacuum. Result: 4.5g, M.P.: 77°C.

Example 26

3-(phenylcarbamoyl)-7-(4-chlorbenzyl)-3.7-diaza-bicyclo[3.3.1]nonan

18.7g (55.7 mmol) of 7-benzyl-3-(phenylcarbamoyl)-3.7-diazabicyclo[3.3.1]nonan is dissolved in 170ml of methanol and 30ml of pure acetic acid. 1.1g of palladium/carbon (10%) is mixed in and hydrated at room temperature for equimolar hydrogen use. This is then filtered and the filtrate is alkalised with sodium hydroxide and constricted in the vacuum. The residue is extracted (x 3) with methylene chloride. The arising organic phase is dried and constricted in the vacuum. This is then crystallised to acetic ester. Result: 8.7g.

3.5g (14.3 mmol) of the resulting amine, 3.2g (20.0 mmol) of 4-chlorbenzylchloride and 5ml of triethylmine are dissolved in 50ml of methanol and left to settle at room temperature for 60 hours. It is then heated for 2 hours at 60°C. The reaction mixture is then made into a weak alkali with sodium hydroxide and constricted in the vacuum. The residue is extracted (x 3) with methylene chloride, the organic phase is dried, and constricted in the vacuum. The solution is then crystallised to acetic ester. Result: 2.0g, M.P.: 161°C.

Analog example 26 produces:

27. 7-(4-nitrobenzyl)-3-(phenycarbamol)-3.7-dichlorbenzyl)-3.7-diaza-bicyclo[3.3.1]nonan, M.P.: 187°C (xHCl)

Example 28

7-benzyl-3-(4-chlorbenzoyl)-3.7-diazabicyclo[3.3.1]-9-nonon

32.0g (0.1 mol) of 3.7-dibenzyl-3.7-diazabicyclo[3.3.1]-9-nonon is mixed with 1g palladium/carbon (10%) and hydrated for equimolar hydrogen use. This is then filtered and the filtrate is constricted in the vacuum. This produces 14.1g of 3-benzyl-3.7-diazabicyclo[3.3.1]-9-nonon. M.P.: 110°C.

14.0g (60.9 mmol) of the above product is dissolved in 100ml of 100ml methylene chloride, mixed with 100ml of 2 M sodium hydroxide and cooled with ice. 16.0g (91.3 mmol) of 4-chlorbenzoylchloride is dissolved in methylene chloride, dripped and left for a further 3 minutes. The organic phase is separated, washed with sodium hydroxide and water, dried and constricted in the vacuum. Result: 22g, M.P.: 154°C (xHCl).

Example 29

7-benzyl-3-(4-chlorbenzoyl)-3.7-diazabicyclo[3.3.1]-9-nonol

14.2g (38.5 mmol) of the ketone made in example 28 is dissolved in 150ml of methanol and mixed in portions to 1.5g (39.5 mmol) of sodium borohydride. The solution is left for 1 hour at RT to settle and 70ml of 1 M hydrochloric acid is added in drops. The solution is constricted in the vacuum, the residue dissolved in methylene chloride, washed with sodium hydroxide and water, then dried and constricted. Result: 14 g, M.P.: 167°C.

Example 30

7-benzyl-3-(4-chlorbenzoyl)-3.7-diaza-bicyclo[3.3.1]-9-nonylbenzoate

3.0g (8.1 mmol) of the above alcohol is dissolved in 50ml of pyridine. At 5-10°C, drop a solution of 2.3g (16.2 mmol) of benzoylchloride into 30ml of pyridine. Leave this overnight to settle. Dilute the reaction mixture with 500ml of water and extract (x 2) with CH_2CI_2. The organic phase is washed with water, dried and constricted. The residue is re-crystallised to acetic ester. Result: 2.0g, M.P.: 165°C.

Example 31

7-benzyl-3-(4-nitrobenzoyl)-3.7-diazabicyclo[3.3.1]-9-nonon

11.3g (49.1 mmol) of 7-benzyl-3.7-diazabicyclo[3.3.1]-9-nonon is dissolved in 100ml methylene chloride and mixed with 100ml of 2 M sodium hydroxide. At 0°C, a solution of 13.7g (73.7 mmol) of 4-nitrobenzoylchloride is dropped into 30ml of methylene chloride and left for 1 hour. The organic phase is separated, washed with water, dried and constricted. The residue is re-crystallised to acetone. 10.5g is produced, M.P.: 138°C.

Example 32

7-benzyl-3-(4-nitrobenzoyl)-3.7-diazabicyclo[3.3.1]-9-nonol

15.0g (39.6 mmol) of the ketone produced in example 31 is dissolved in 150ml of methanol. At room temperature, steadily add 1.5g (39.6 mmol) of sodium borohydride and leave for 1 hour. Then, drop 50ml of 2 M hydrochloric acid into the solution and leave for 2 hours at room temperature, then constrict the mixture in the vacuum. The residue is divided between methylene chloride and sodium hydroxide, the organic phase separated, again with sodium hydroxide, then washed with water, dried and constricted. It is crystallised to acetic ester and 11.5g is produced, M.P.: 210°C.

Example 33

7-benzyl-3-(4-nitrobenzoyl)-3.7-diazabicyclo[3.3.1]-9-nonylbenzoate

4.0g (10.5 mmol) of the alcohol produced in example 32 is dissolved in 50ml of pyridine. At 5-10°C, 3.0g (21 mmol) of benzoylchloride is dropped in and the solution is left for 3 hours at room temperature. The reaction mixture is then diluted using 500ml of water and extracted (x 2) with ether. The organic phase is washed (x 2) with water, dried and constricted. The resulting residue is crystallised to acetic ester. 3.8g is produced, M.P.: 180°C.

Example 34

3-(4-aminob nzoyl)-7-benzyl-3.7-diazabicyclo[3.3.1]-9-nonylbenzoate

3.8g (7.8 mmol) of the ester produced in example 33 is dissolved in 250ml of methanol with platinum/carbon and hydrated at room temperature. This is then filtered and the filtrate is constricted in the vacuum. By crystallising the residue to acetic ester, 1.1g is produced, M.P.:99°C.
Through catalytic hydration, analogue example 34 produces:

35. 3-(4-aminobenzoyl)-7-benzyl-3.7- diaza-bicyclo[3.3.1]-9-nonon, M.P.: 235°C (xHCl)
36. 3-(4-aminobenzoyl)-7-benzyl-3.7-diaza-bicyclo[3.3.1]-9-nonol, M.P.: 232°C (x2HCl)

Example 37

7-benzyl-3-(4-chlorbenzoyl)-ethyl-3.7- diaza-bicyclo[3.3.1]-9-nonol

At room temperature, drop a solution of 5.0g (13.6 mmol) of 7-benzyl-3-(4-chlorbenzoyl)-3.7-diazabicyclo-[3.3.1]-9-nonon (example 28) and 50ml of anhydrous tetrahydrofurane into the Grignard reagent of 0.7g (27.2 mmol) of magnesium and 3.4g of ethylbromide. Leave for 1 hour, then hydrolise with 50ml water and less than 2 M hydrochloric acid. The mixture is constricted in the vacuum. The residue is divided between methylene chloride and 2 M sodium hydroxide, the organic phase separated, washed again with 2 M sodium hydroxide and water, dried and constricted. Result: 3.4g, M.P.: 72°C.

Claims

1. Formula 1 bispidine

[DIAGRAM]

where
R, R^1 and R^3 are the same or different and represent H, C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy and
when

Y = - C-,
R^2 represents C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy, - $NHSO_2CH_3$, $-CF_3$, NH-acetyl and $-NR^4R^5$, where R^4 and R^5 are C_1-C_4-alkyl and represent C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy, $-NHSO_2CH_3$, $-CF_3$, NH-acetyl and $-NR^9R^{10}$ when

Y = - C-NH-,
Where NR^9 represents C_1-C_4-alkyl and R^{10} represents H or C_1-C_4-alkyl and R^2 can also be NO_2 and NH_2 when X = CH_2.

X represents $-CH_2-$, -C(O)- or $-C(R^6)OR^7-$ (where R^6 represents H, C_1-C_4-alkyl and R^7 represents H, C_1-C_4-alkyl and

[DIAGRAM]

with R^8 representing H. C_1-C_4-alkyl, halogen or C_1-C_4-alkoxy),
Y can be -C(O)- or -CONH- and
Z can be , C_1-C_4-alkyls, which are unsaturated and/or can be branched, as well as their physiologically digestible salts.

2. Bispidine derivatives according to claim 1, characterised by the fact that Y shows the -CONH- rest.

3. Medicine, which contains a bispidine derivative according to claim 1 as a catalyst alongside the normal auxiliary materials.

4. Medicine for topical use, which contains between 0.0001 and 1 by weight % of a bispidine derivative according to claim 1 alongside the normal auxiliary materials.

5. Medicine for para-oral use, which contains between 5mg and 200mg per single dose a bispidine derivative according to claim 1 alongside the normal auxiliary materials.

6. Medicine for oral use, which contains between 50mg and 1000mg per single dose a bispidine derivative according to claim 1 alongside the normal auxiliary materials.

7. Use of a reagent according to claim 1 for the production of medicine.

8. Use of a reagent according to claim 1 for the production of a class III (Vaughn Williams) anti-arrythmic.